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**Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline**

A Report of the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes and its Panel on Folate, Other B Vitamins, and Choline and Subcommittee on Upper Reference Levels of Nutrients, Food and Nutrition Board, Institute of Medicine

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# 12
# Choline

## SUMMARY

Choline functions as a precursor for acetylcholine, phospholipids, and the methyl donor betaine. The primary criterion used to estimate the Adequate Intake (AI) for choline is the prevention of liver damage as assessed by measuring serum alanine aminotransferase levels. The AI for adults is 550 mg/day of choline for men and 425 mg/day for women. There are no nationally representative estimates of the intake of choline from food or food supplements. Choline in the diet is available as free choline or is bound as esters such as phosphocholine, glycerophosphocholine, sphingomyelin, or phosphatidylcholine. The critical adverse effect from high intake of choline is hypotension, with corroborative evidence on cholinergic side effects (e.g., sweating and diarrhea) and fishy body odor. The Tolerable Upper Intake Level (UL) for adults is 3.5 g/day.

## BACKGROUND INFORMATION

Choline is a dietary component that is important for the structural integrity of cell membranes, methyl metabolism, cholinergic neurotransmission, transmembrane signaling, and lipid and cholesterol transport and metabolism. Human cells grown in culture have an absolute requirement for choline (Eagle, 1955). When cells are deprived of choline, they die by apoptosis (Albright et al., 1996; Cui et al., 1996; Holmes-McNary et al., 1997; James et al., 1997; Shin et



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al., 1997; Zeisel et al., 1997). There is an endogenous pathway for the de novo biosynthesis of the choline moiety via the sequential methylation of phosphatidylethanolamine using *S*-adenosylmethionine as the methyl donor (Bremer and Greenberg, 1961) (see Figure 12-1). Thus, the demand for dietary choline is modified by metabolic methyl-exchange relationships between choline and three nutrients: methionine, folate, and vitamin $B_{12}$ (lipotropes) (Zeisel and Blusztajn, 1994).

With this type of nutrient interdependence, designation of the essential nature of a nutrient depends on showing that de novo synthesis rates are not adequate to meet the demand for the nutrient when the other nutrients are available in amounts sufficient to sustain normal growth and function. Healthy men with normal folate and vitamin $B_{12}$ status fed a choline-deficient diet have diminished plasma choline and phosphatidylcholine concentrations and develop liver damage (Zeisel et al., 1991). For these individuals, de novo synthesis of choline was not adequate to meet the demand for

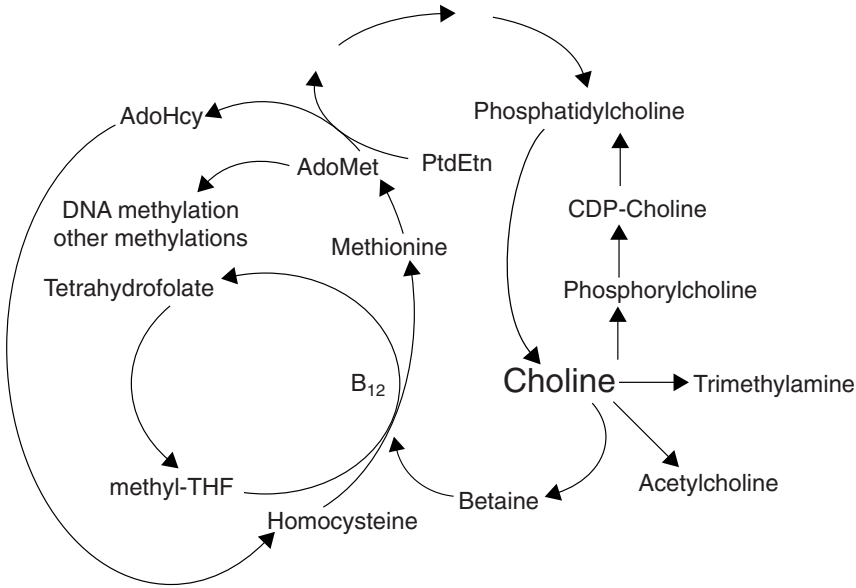


**FIGURE 12-1** Choline, folate, and methionine metabolism are closely interrelated. AdoHcy = *S*-adenosylhomocysteine, AdoMet = *S*-adenosylmethionine, $B_{12}$ = vitamin $B_{12}$, CDP-Choline = cytidine diphosphocholine, PtdEtn = phosphatidylethanolamine, THF = tetrahydrofolate. Reprinted with permission, from Zeisel and Blusztajn (1994). Copyright 1994 by Annual Reviews.

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the nutrient. Information about women, infants, children, and older adults is not sufficient to know whether choline is needed in the diet of these groups.

### *Function*

Choline can be acetylated, phosphorylated, oxidized, or hydrolyzed. Several comprehensive reviews of the metabolism and functions of choline have been published (Kuksis and Mookerjea, 1978; Zeisel, 1981; Zeisel and Blusztajn, 1994).

Choline accelerates the synthesis and release of acetylcholine, an important neurotransmitter involved in memory storage, muscle control, and many other functions (Cohen and Wurtman, 1975; Haubrich et al., 1974; Wecker, 1986). It is also a precursor for the synthesis of (1) phospholipids, including phosphatidylcholine (a membrane constituent important for the structure and function of membranes), for intracellular signaling (Exton, 1994; Zeisel, 1993) and hepatic export of very low-density lipoproteins (Yao and Vance, 1988, 1989); (2) sphingomyelin (another membrane constituent) for structural and signaling functions (Hannun, 1994); and (3) platelet activating factor, a potent messenger molecule (Frenkel et al., 1996). Choline is a precursor for the formation of the methyl donor betaine. Betaine is also required by renal glomerular cells, which use betaine and glycerophosphocholine as organic osmolytes to adapt to osmotic stress (Bauernschmitt and Kinne, 1993; Burg, 1995; Garcia-Perez and Burg, 1991; Grossman and Hebert, 1989).

### *Physiology of Absorption, Metabolism, and Excretion*

Dietary choline is absorbed from the lumen of the small intestine via transporter proteins in the enterocyte (Herzberg and Lerner, 1973; Herzberg et al., 1971; Kuczler et al., 1977; Sheard and Zeisel, 1986). Before choline can be absorbed from the gut, some is metabolized by bacteria to form betaine (which may be absorbed and used as a methyl donor) and methylamines (which are not methyl donors) (Zeisel et al., 1983). No other component of the diet has been identified as competing with choline for transport by intestinal carriers. Choline is found in foods as free choline and as esterified forms such as phosphocholine, glycerophosphocholine, sphingomyelin, and phosphatidylcholine. Lecithin is a phosphatidylcholine-rich fraction prepared during commercial purification of phospholipids, and this term is often used interchangeably with phosphatidylcholine. Lecithin is often added to foods as an emulsifying agent.

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Pancreatic enzymes can liberate choline from dietary phosphatidylcholine, phosphocholine, and glycerophosphocholine (Zeisel and Blusztajn, 1994). The free choline that is formed enters the portal circulation of the liver (Le Kim and Betzing, 1976) whereas phosphatidylcholine may enter via lymph in chylomicrons.

All tissues accumulate choline by diffusion and mediated transport (Zeisel, 1981). A specific carrier mechanism transports free choline across the blood-brain barrier at a rate that is proportional to the serum choline concentration. In the neonate this choline transporter has an especially high capacity (Cornford and Cornford, 1986). The rate at which the liver takes up choline is sufficient to explain the rapid disappearance of choline injected systemically (Zeisel et al., 1980c). The kidney also accumulates choline (Acara and Rennick, 1973). Some of this choline appears in the urine unchanged but most is oxidized within the kidney to form betaine (Rennick et al., 1977).

In the predominant pathway for phosphatidylcholine biosynthesis, choline is phosphorylated, converted to cytidine diphosphocholine, and then converted to phosphatidylcholine (Kennedy and Weiss, 1956; Vance, 1990) (Figure 12-1). In an alternative pathway, phosphatidylethanolamine is sequentially methylated to form phosphatidylcholine by the enzyme phosphatidylethanolamine-*N*-methyltransferase with *S*-adenosylmethionine as the methyl donor (Bremer and Greenberg, 1961; Vance and Ridgway, 1988). This is the major (perhaps only) pathway for de novo synthesis of the choline moiety in adult mammals. It is most active in the liver but has been identified in many other tissues (Blusztajn et al., 1979; Crews et al., 1981; Yang et al., 1988). Best estimates of in vivo activity of this enzyme, based on in vitro data, are that 15 to 40 percent of the phosphatidylcholine present in the liver is derived from the phosphatidylethanolamine-*N*-methyltransferase pathway, with the remainder coming from the cytidine diphosphocholine pathway (Bjornstad and Bremer, 1966; Sundler and Akesson, 1975). No estimates are available as to the relative extent of choline obtained from cell turnover. Dietary intake of phosphatidylcholine is approximately 6 to 10 g/day (Zeisel et al., 1991).

A significant portion of choline is oxidized to form betaine in the liver and kidney (Bianchi and Azzone, 1964; Weinhold and Sanders, 1973). The methyl groups of betaine can be scavenged and reused in single-carbon metabolism (Finkelstein et al., 1982) (see "Nutrient-Nutrient Interactions").

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## *Clinical Effects of Inadequate Intake*

### *Humans*

Although choline is clearly essential to life, there is only one published study examining the effects of inadequate dietary intake in healthy men. That study reported decreased choline stores and liver damage (elevated alanine aminotransferase) when men were fed a choline-deficient diet containing adequate methionine, folate, and vitamin $B_{12}$ for 3 weeks (Zeisel et al., 1991) (Figures 12-2 and 12-3). Another study, in which men were fed a choline- and methyl-deficient diet, reported decreased choline stores but did not report on liver function (Jacob et al., 1995). Individuals fed with total parenteral nutrition (TPN) solutions devoid of choline but adequate for methionine and folate develop fatty liver and liver damage as assessed by elevated alanine aminotransferase; in some individu-

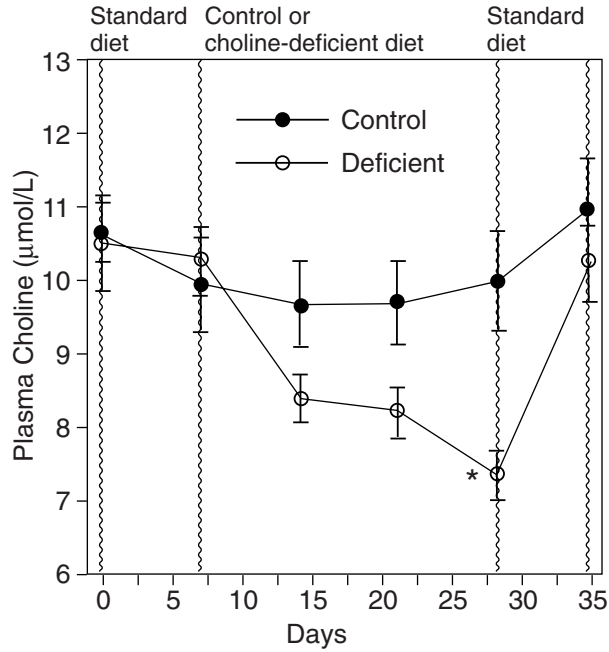


**FIGURE 12-2** Plasma choline in healthy men ingesting a control (500 mg/day of choline) or choline-deficient (13 mg/day of choline) diet. *Difference from day 7 value: $p < 0.01$. Reprinted with permission, from Zeisel et al. (1991). Copyright 1991 by the Federation of American Societies for Experimental Biology.

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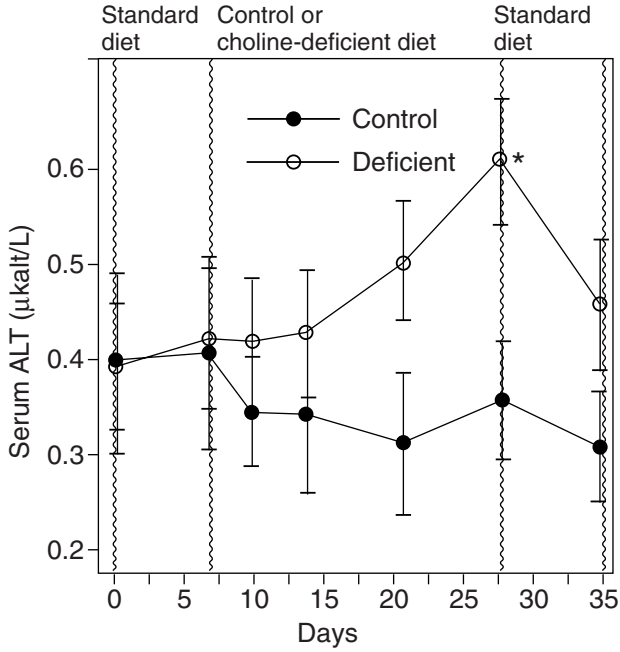


**FIGURE 12-3** Serum alanine aminotransferase (ALT) activity in men ingesting a control or choline-deficient diet. Serum ALT was determined by using an automated spectrophotometric assay. Data are expressed as mean activity ± standard error of the mean. *Difference from day 7 value: $p < 0.05$. Reprinted with permission, from Zeisel et al. (1991). Copyright 1991 by the Federation of American Societies for Experimental Biology.

als, this is resolved when a source of dietary choline is provided (Buchman et al., 1992, 1993, 1995; Chawla et al., 1989; Shapira et al., 1986; Sheard et al., 1986). In a double-blind protocol, investigators administered lecithin (30 percent phosphatidylcholine) orally to patients receiving TPN twice daily for 6 weeks. At the end of this time, plasma choline had risen by more than 50 percent in the lecithin group whereas in the placebo group it had decreased by 25 percent. In the treated group, liver fat decreased by 30 percent (Buchman et al., 1992). In another small clinical study (Buchman et al., 1995), four patients who had low plasma concentrations of free choline after treatment with TPN (which contained no additional choline) were given 1 to 4 g/day of choline chloride for 6 weeks. During choline administration, plasma choline concentration

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increased into the normal range but decreased back to baseline when choline supplementation was discontinued. Fatty liver was resolved completely during choline supplementation but steatosis (fatty liver) recurred in one patient after 10 weeks of return to choline-free TPN. The available data support the provisional conclusion that de novo synthesis of choline is not always sufficient to meet human requirements for choline.

### *Animals*

Supporting animal studies (in many species, such as the baboon) also found that a choline-deficient diet resulted in decreased choline stores and liver dysfunction (Hoffbauer and Zaki, 1965; Sheard et al., 1986; Tayek et al., 1990; Yao and Vance, 1990). The following animals fed a choline-deficient diet may be susceptible to developing growth retardation, renal dysfunction and hemorrhage, or bone abnormalities: baboon (Hoffbauer and Zaki, 1965), chicken (Blair et al., 1973; Ketola and Nesheim, 1974), dog (Best and Huntsman, 1932; Hershey, 1931), guinea pig (Tani et al., 1967), hamster (Handler, 1949), pig (Blair and Newsome, 1985; Fairbanks and Krider, 1945), quail (Ketola and Young, 1973), rat (Newberne and Rogers, 1986), and trout (Ketola, 1976).

## SELECTION OF INDICATORS FOR ESTIMATING THE REQUIREMENT FOR CHOLINE

### *Markers of Liver Dysfunction*

The liver is damaged when humans consume an otherwise adequate diet that is deficient in choline, resulting in elevated alanine aminotransferase levels in blood (Burt et al., 1980; Tayek et al., 1990; Zeisel et al., 1991). Fatty infiltration of liver also occurs in choline deficiency but is difficult to use as a functional marker without special liver imaging techniques (Buchman et al., 1992).

Hepatic choline and choline metabolite concentrations have been shown to decrease during choline deficiency in the rat (Zeisel et al., 1989). Phosphocholine concentration in liver is highly correlated with dietary choline intake, decreasing to 10 to 20 percent of control values after 2 weeks on a diet sufficient in methionine, folate, and vitamin $B_{12}$ but deficient in choline (Pomfret et al., 1990). Hepatic phosphocholine concentration was most sensitive to modest dietary choline deficiency, decreasing to 10 to 20 percent of control values after 2 weeks of a deficient diet (Pomfret et al., 1990). This

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measurement is not easily undertaken in humans, although magnetic resonance spectroscopy does makes it possible (Cohen et al., 1995).

### *Plasma Concentrations*

Plasma choline concentration varies in response to diet and is found in the water-soluble fraction as free choline (Buchman et al., 1993; Burt et al., 1980; Chawla et al., 1989; Sheard et al., 1986; Zeisel et al., 1991). It decreases approximately 30 percent in subjects fed a choline-deficient diet for 3 weeks (Zeisel et al., 1991). Plasma choline concentration can increase twofold after a meal high in choline content and three- or fourfold after a supplemental choline dose (Zeisel et al., 1980b). Fasting plasma choline concentrations vary from 7 to 20 μmol/L, with most subjects having concentrations of 10 μmol/L. The disadvantage of using plasma choline as a functional indicator is that these concentrations do not appear to decline below approximately 50 percent of normal, even when subjects fast for more than 1 week (Savendahl et al., 1997). Perhaps this is because membrane phospholipids, which are a large storage pool for choline, are hydrolyzed to maintain plasma choline concentration above this minimal level. Fasting plasma phosphatidylcholine concentrations (mostly as part of plasma lipoproteins) are approximately 1 to 1.5 mmol/L (Aquilonius et al., 1975; Zeisel et al., 1980b, 1991). Plasma phosphatidylcholine concentration also decreases in choline deficiency (Zeisel et al., 1991) but is also influenced by factors that change plasma lipoprotein levels.

### *Reduction of Risk of Chronic Disease*

#### *Dementia*

Studies in rodents suggest that dietary intake of choline early in life can diminish the severity of memory deficits in aged animals (Bartus et al., 1980; Meck and Williams, 1997a, b, c). Most available human studies have used choline-containing compounds to treat rather than prevent the symptoms of dementia and therefore did not address whether dementias could be prevented. In the absence of food composition data, epidemiological studies on the association of choline intake with dementia are not available. More human studies are needed to determine whether dietary choline intake is useful in the prevention of dementia.

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### *Cardiovascular Disease*

The choline-containing phospholipid phosphatidylcholine (lecithin) has been used as a treatment to lower cholesterol concentrations because lecithin-cholesterol acyltransferase has an important role in the removal of cholesterol from tissues. In humans phosphatidylcholine ingestion is associated with a modest reduction in plasma cholesterol (Hirsch et al., 1978; Wood and Allison, 1982; Zeisel et al., 1991). In addition, choline or betaine treatment has been used to lower high plasma homocysteine concentrations (Anonymous, 1997; Dudman et al., 1987; Wendel and Bremer, 1984; Wilcken et al., 1983, 1985), and choline-deficient rodents have elevated plasma homocysteine concentrations (Varela-Moreiras et al., 1995) (see Chapter 8, "Vascular Disease"). Wendel and Bremer (1984) reported that betaine treatment was more effective than folate treatment in normalizing plasma homocysteine and methionine concentrations of a child with homocystinuria, a genetic disease caused by 5,10-methylenetetrahydrofolate reductase deficiency (choline is the precursor for betaine, which itself is found in sugar beets and wine). Therefore, dietary choline intake might be correlated with cardiovascular disease risk. More human studies are needed before conclusions can be drawn about whether dietary choline intake is useful in preventing cardiovascular disease.

### *Cancer*

In rodents dietary choline deficiency is associated with increased incidence of liver cancer and increased sensitivity to carcinogenic chemicals (Newberne and Rogers, 1986). The mechanisms of the carcinogenic actions of choline deficiency are not known but may be mediated by changes in protein kinase C activity (da Costa et al., 1993, 1995). There are no human data; studies in humans are needed to assess the role of dietary choline in the prevention of cancer.

## FACTORS AFFECTING THE CHOLINE REQUIREMENT

### Nutrient-Nutrient Interactions

Any consideration of the requirements for choline and methionine needs to include the close interrelationships with other methyl donors. Choline, methionine, and folate metabolism interact at the point that homocysteine is converted to methionine.

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Betaine-homocysteine methyltransferase catalyzes the methylation of homocysteine using betaine as the methyl donor (see Figure 12-1) (Finkelstein et al. 1982; Mudd and Poole, 1975; Wong and Thompson, 1972). In an alternative pathway, 5-methyltetrahydrofolate-homocysteine methyltransferase regenerates methionine by using a methyl group derived de novo from the single-carbon pool (Finkelstein et al., 1982, 1988). Methionine adenosyltransferase converts methionine to *S*-adenosylmethionine (the active methylating agent for many enzymatic methylations, including the methylation of phosphatidylethanolamine to form phosphatidylcholine [Ridgway and Vance, 1988]).

Perturbing the metabolism of one of the methyl donors reveals the intermingling of these metabolic pathways. Total hepatic folate content decreased by 31 to 40 percent in rats after 2 weeks on a choline-deficient diet (Selhub et al., 1991; Varela-Moreiras et al., 1995). This effect was reversed by refeeding choline (Varela-Moreiras et al., 1995). Rats fed diets deficient in both methionine and choline for 5 weeks had hepatic folate concentrations that were half of those present in controls (Horne et al., 1989). Tetrahydrofolate deficiency in rats, induced by treatment with methotrexate (Barak and Kemmy, 1982; Barak et al., 1984; Freeman-Narrod et al., 1977; Pomfret et al., 1990; Svardal et al., 1988) or by dietary folate deficiency (Kim et al., 1994) resulted in diminished hepatic total choline, with the greatest decrease occurring in hepatic phosphocholine concentrations. During choline deficiency in rats, hepatic *S*-adenosylmethionine concentrations also decreased by as much as 50 percent (Barak et al., 1982; Poirier et al., 1977; Shivapurkar and Poirier, 1983; Zeisel et al., 1989). In rats choline deficiency for 2 weeks doubled plasma homocysteine levels (Varela-Moreiras et al., 1995). See Chapters 7 and 8 for more information on plasma homocysteine.

### *Gender*

Males may have a higher choline requirement than do females. Female rats are less sensitive to choline deficiency than are male rats (Tessitore et al., 1995), perhaps because of females' enhanced capacity to form the choline moiety de novo. Females rats have greater phosphatidylethanolamine-*N*-methyltransferase activity in liver than do males (Arvidson, 1968; Bjornstad and Bremer, 1966; Lyman et al., 1971). Estimates of the amount of increased activity vary between 10 (Lyman et al., 1971) and 50 percent (Bjornstad and Bremer, 1966). A woman's capacity to form the choline moiety

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de novo may decrease after menopause (Lindblad and Schersten, 1976), because estrogens increase hepatic phosphatidylethanolamine-*N*-methyltransferase activity in rats (Drouva et al., 1986; Young, 1971).

### *Exercise*

Strenuous physical activity in trained athletes reduced the plasma choline concentration by approximately 40 percent, from 14.1 to 8.4 μmol/L (Conlay et al., 1986). A choline supplement given to marathon runners modestly enhanced performance (Sandage et al., 1992). In 10 top-level triathletes who were given either a placebo or lecithin at 0.2 g/kg body mass 1 hour before each type of exercise, plasma choline concentrations in all the triathletes decreased on average by 16.9 percent after the bicycle exercise when placebo was taken before the race but did not do so when lecithin was given (Von Allworden et al., 1993).

### *Bioavailability*

No estimates are available for percentage absorption of the various forms of choline in humans. The water-soluble choline-derived compounds (choline, phosphocholine, and glycerophosphocholine) are absorbed via the portal circulation whereas the lipid-soluble compounds (phosphatidylcholine and sphingomyelin) present in foods are absorbed into lymph as chylomicrons via the thoracic duct. This results in differential delivery and kinetics of distribution to tissues (Cheng et al., 1996; Zeisel et al., 1980b).

## FINDINGS BY LIFE STAGE AND GENDER GROUP

Data are not sufficient for deriving an Estimated Average Requirement (EAR) for choline. The two published studies in healthy humans used male subjects only and tested a single level of choline intake. For these reasons only an Adequate Intake (AI) can be estimated. This amount will be influenced by the availability of methionine and folate in the diet. It may be influenced by gender, pregnancy, lactation, and stage of development. Although AIs are set for choline, it may be that the choline requirement can be met by endogenous synthesis at some of these stages.

To date, all studies have used choline-free diets and compared them with choline-containing diets; no intermediate levels of defi-

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ciency have been reported. Careful dose-response experiments are needed before an EAR can be derived.

### *Infants Ages 0 through 12 Months*

#### *Method Used to Set the AI*

An AI is used as the goal for intake by infants.

*Ages 0 through 6 Months.* The AI reflects the observed mean intake of choline by infants consuming human milk. Thus the choline AI for young infants is based on mean intake data from infants fed human milk exclusively for their first 6 months and uses the choline concentration of milk produced by well-nourished mothers. Human milk contains 160 to 210 mg (1.5 to 2 mmol)/L of choline moiety delivered as choline, phosphocholine, glycerophosphocholine, phosphatidylcholine, and sphingomyelin (Holmes-McNary et al., 1996; Zeisel et al., 1986). The choline phospholipids sphingomyelin and phosphatidylcholine are part of the milk fat-globule membrane (Holmes-McNary et al., 1996; Zeisel et al., 1986).

Rat pups denied access to milk have lower serum choline concentrations than do their fed litter mates (Zeisel and Wurtman, 1981). Thus, milk intake contributes to the maintenance of high serum choline concentrations in the neonate. In the rat, supplemental choline is concentrated in the rat dam's milk (Garner et al., 1995; Zeisel, 1987). In women consuming a low-choline diet, milk choline content is lower than that in women consuming a more adequate diet (Zeisel et al., 1982). Consumption of either a choline-deficient or choline-supplemented diet by lactating rat dams results in significant changes in the phosphocholine concentration of their milk (Holmes-McNary et al., 1996; Zeisel et al., 1986).The concentration of total choline in human milk is 160 mg/L (1.5 mmol/L). For the mean volume of output of human milk of 0.78 L/day and the average choline content of 160 mg/L, the AI for choline is 125 mg/day (1.2 mmol/day) for infants ages 0 through 6 months. For the reference infant weight of 7 kg, this corresponds to an AI of 18 mg/kg of body weight/day (0.17 mmol/kg/day).

*Ages 7 through 12 Months.* If the reference body weight ratio method described in Chapter 2 to extrapolate from the AI for choline for infants ages 0 through 6 months is used, the AI for choline for the older infants would be 150 mg/day (1.4 mmol/day). The second method (see Chapter 2), extrapolating from the AI for adults, gives

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an AI that is essentially the same as that from extrapolating from infants. There are no data estimating choline intake from foods for this age group.

*Choline AI Summary, Ages 0 through 12 Months*

| **AI for Infants** | | |
|---|---|---|
| **0–6 months** | **125 mg/day of choline** | **≈18 mg/kg** |
| **7–12 months** | **150 mg/day of choline** | **≈17 mg/kg** |

*Special Considerations*

Although commercially available infant formulas and bovine milk both contain choline and choline-containing compounds (Holmes-McNary et al., 1996; Rohlfs et al., 1993; Zeisel et al., 1986), human milk has a significantly higher phosphocholine concentration (718 μmol/L) than does either cow milk or infant formulas. However, cow milk and cow-milk-derived infant formulas have the same glycerophosphocholine concentration as human milk (400 to 800 μmol/L) (Holmes-McNary et al., 1996) or higher (415 μmol/L) (Holmes-McNary et al., 1996). Soy-derived infant formulas have lower glycerophosphocholine concentration (115 μmol/L or less) (Holmes-McNary et al., 1996). Human milk phosphatidylcholine and sphingomyelin concentrations do not differ significantly from those in cow milk and cow-milk-derived infant formulas (200 μmol/L) (Holmes-McNary et al., 1996). Soy-derived infant formulas contain more phosphatidylcholine than do either human milk or cow-milk-derived formulas but less sphingomyelin than human milk (Holmes-McNary et al., 1996). Unesterified choline concentration in mature human milk is 30 to 80 percent lower than in either cow milk or the infant formulas (Holmes-McNary et al., 1996). The relative bioavailability of choline, phosphocholine, and glycerophosphocholine is similar in a rat model (Cheng et al., 1996) but no information is available for humans. Thus, it is not known whether these differences in milk and formula composition are clinically relevant.

### *Children and Adolescents Ages 1 through 18 Years*

*Method Used to Set the AI*

No direct data on choline were found on which to base an EAR or AI for children and adolescents. In the absence of additional infor-

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mation, AIs for these age groups have been extrapolated from adult values by using the method described in Chapter 2.

*Choline AI Summary, Ages 1 through 18 Years*

| | | |
|---|---|---|
| **AI for Children** | **1–3 years** | **200 mg/day of choline** |
| | **4–8 years** | **250 mg/day of choline** |
| **AI for Boys** | **9–13 years** | **375 mg/day of choline** |
| | **14–18 years** | **550 mg/day of choline** |
| **AI for Girls** | **9–13 years** | **375 mg/day of choline** |
| | **14–18 years** | **400 mg/day of choline** |

### *Adults Ages 19 Years and Older*

*Method Used to Set the AI*

An intake level of 500 mg/day (4.8 mmol/day; approximately 7 mg/kg/day [0.7mmol/kg/day]) of choline base is the dose that prevented alanine aminotransferase abnormalities in healthy men (Zeisel et al., 1991). This estimate for an AI is uncertain because it is based on a single published study; it may need revision when other data become available. This estimate fits within the bracketing estimates derived from patients on total parenteral nutrition for whom approximately 2 mg/kg/day of choline moiety did not prevent a deficiency syndrome (Sheard et al., 1986) and 31 mg/kg/day of choline moiety restored normal choline status (Buchman et al., 1992, 1993). The amount estimated as adequate for men should be sufficient to prevent an increase in alanine aminotransferase but it resulted in a small decrease in plasma choline in the one study in which it was evaluated, which suggests that dietary intake normally might be slightly higher. Thus the AI is set at approximately 7 mg/kg/day or, for the reference man weighing 76 kg, at 550 mg after rounding.

To arrive at an estimate for AI for women, it is assumed that data from men can be used even though women may use choline more efficiently (see "Gender"). No experimental attempts to make healthy women choline deficient have been reported. However, women on total parenteral nutrition were just as likely as were men to develop low plasma choline concentrations and fatty liver (Buchman et al., 1995).

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No experimental data are available from which to calculate an AI for life stage groups other than adults as a whole.

### *Choline AI Summary, Ages 19 Years and Older*

The AI for choline in all forms for men in all age groups is 550 mg and for women is 425 mg. It is not known whether women have the same requirement on a body weight basis as men, but this AI is likely to be adequate on the basis of the earlier discussion on gender. Although there is some evidence that transport across the blood-brain barrier is diminished in the elderly, which suggests the possibility of a higher requirement than for younger adults (Cohen et al., 1995), no adjustment has been made in the AI for the elderly.

| | | |
|---|---|---|
| **AI for Men** | **19–30 years** | **550 mg/day of choline** |
| | **31–50 years** | **550 mg/day of choline** |
| | **51–70 years** | **550 mg/day of choline** |
| | **> 70 years** | **550 mg/day of choline** |
| **AI for Women** | **19–30 years** | **425 mg/day of choline** |
| | **31–50 years** | **425 mg/day of choline** |
| | **51–70 years** | **425 mg/day of choline** |
| | **> 70 years** | **425 mg/day of choline** |

## *Pregnancy*

### *Evidence Considered in Setting the AI*

The need for choline is probably higher for pregnant than for nonpregnant women on the basis of animal data. Pregnancy renders female rats as vulnerable to deficiency as males (Zeisel et al., 1995). During pregnancy in humans (Welsch 1978; Welsch et al., 1981), guinea pigs (Swiery and Yudilevich, 1985; Swiery et al., 1986; Yudilevich and Sweiry, 1985), and rats (Jorswieck, 1974) large amounts of choline are delivered to the fetus through the placenta. Transport of choline from mother to fetus depletes maternal stores of choline; the choline concentration of maternal liver fell from a mean of 130 μmol/L in adult nonpregnant rats to 38 μmol/L in late pregnancy (Gwee and Sim, 1978).

Choline availability during embryogenesis and perinatal development may be especially important. In rats fed adequate diets during pregnancy, postnatally, and at weaning, 1 mmol/day of extra dietary choline results in long-lasting enhancement of spatial memory

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(Meck and Williams, 1997a, b, c), altered morphology of septal neurons (Loy et al., 1991; Williams et al., 1998), and enhanced hippocampal long-term potentiation (Pyapali et al., 1998) and cholinergic neurotransmission (Cermak et al., 1998; Holler et al., 1996). The two periods of sensitivity to extra choline occur during embryonic days 12 to 17 and postnatal days 16 to 30 (Loy et al., 1991; Meck et al., 1988, 1989).

In mammals the placenta transports choline to the fetus (Welsch, 1976); choline concentration in amniotic fluid is 10-fold greater than that in maternal blood (S. Zeisel, University of North Carolina School of Public Health, unpublished observations, 1997). At birth, humans and other mammals have plasma choline concentrations that are much higher than those in adults (Zeisel et al., 1980a). It is not known whether de novo synthesis of choline increases during pregnancy.

The AI for pregnant women is greater than that for the adult by the amount needed for the fetus and placenta. Through the use of published values for the choline concentration of various adult rat tissues (Pomfret et al., 1989) and with the assumption of a body organ weight percentage as estimated by Widdowson (1963) for the human fetus, the fetal choline content can be estimated as approximately 5 mmol/kg (520 mg/kg) fetal weight. Human placental tissue has been estimated to average 1.26 ± 0.24 mmol/kg (mean ± standard error) in a small sample ($n = 7$) (Welsch, 1976); a value of approximately 2 mmol of choline per kg of placental tissue should cover almost all pregnant women. If it is thus assumed that the average choline content of fetal and placental tissue combined is approximately 3 mmol/kg (312 mg/kg), that there is no extra synthesis during pregnancy, and that there is no contribution of choline by placental or fetal synthesis, the required dietary amount of choline for the 10 kg of tissue that comprises the fetus (3 kg) and organs of pregnancy (7 kg) is 30 mmol, or 3,000 mg (10 kg tissue × 312 mg), which is approximately 11 mg/day (10 μmol/day) of additional dietary choline throughout pregnancy. This amount would be achieved by increasing the AI (after rounding) to 450 mg/day of choline for pregnancy.

### *Choline AI Summary, Pregnancy*

The increase in the AI to support pregnancy is based on the fetal and placental accumulation of choline.

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| | | |
|---|---|---|
| **AI for Pregnancy** | **14–18 years** | **450 mg/day of choline** |
| | **19–30 years** | **450 mg/day of choline** |
| | **31–50 years** | **450 mg/day of choline** |

### *Lactation*

#### *Method Used to Set the AI*

The need for choline is likely to be increased during lactation because a substantial amount of choline is secreted in human milk, and mechanisms for conserving maternal choline status have not been identified. Lactating rats are more sensitive to choline deficiency than are nonlactating rats (Zeisel et al., 1995).

The AI for women during the first 6 months of lactation should be increased above that in the nonpregnant, nonlactating woman to cover the choline that is transferred into milk. For the assumption of an average volume production of 0.78 L/day (see Chapter 2) and an average choline content of milk of 156 mg/L (1.5 mmol/L), this increase is 125 mg/day (1.2 mmol/day). This increase is based on an assumption of 100 percent efficiency. It is not known whether de novo synthesis of choline increases during lactation. Women who are breastfeeding older infants who are also eating solid foods may need slightly less because of a lower volume of milk production.

#### *Choline AI Summary, Lactation*

| | | |
|---|---|---|
| **AI for Lactation** | **14–18 years** | **550 mg/day of choline** |
| | **19–30 years** | **550 mg/day of choline** |
| | **31–50 years** | **550 mg/day of choline** |

## INTAKE OF CHOLINE

### *Food Sources*

Choline is widely distributed in foods, with most of it in the form of phosphatidylcholine in membranes. Foods that are especially rich in choline compounds are milk, liver, eggs, and peanuts. It is possible to consume a diet of normal foods that delivers 1 g/day of choline (Zeisel et al., 1980b). Lecithins added during food processing may increase the average daily per capita consumption of phosphatidylcholine by 1.5 mg/kg of body weight for adults (this corre-

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sponds to 0.225 mg/kg of body weight of choline moiety) (SCOGS/LSRO, 1979).

### *Dietary Intake*

Choline intake is not reported in the Third National Health and Nutrition Examination Survey (Perloff et al., 1990), the Continuing Survey of Food Intake by Individuals (Perloff et al., 1990), or the Boston Nutritional Status Survey (Hartz et al., 1992), and the choline content of foods is not included in major nutrient databases. There are no reports on choline intake from Canada. Estimated average choline dietary intake in adults consuming a typical U.S. or Canadian diet (as free choline and the choline in phosphatidylcholine and other choline esters) is approximately 730 to 1,040 mg/day (7 to 10 mmol/day) (LSRO/FASEB, 1981; Zeisel, 1981). Calculations of dietary choline intake are based on estimates of the free choline and phosphatidylcholine content of foods (Engel, 1943; McIntire et al., 1944; Weihrauch and Son, 1983; Zeisel et al., 1986). Older assay procedures for choline were imprecise and did not always include glycerophosphocholine or phosphocholine content, making many of the available data unreliable. On the basis of a finding of decreased plasma choline and phosphatidylcholine concentrations when humans were switched from a diet of normal foods to a defined diet containing 500 mg/day of choline (Zeisel et al., 1991), the average dietary intake of choline probably exceeds this level in adults. Infant formulas contain approximately 240 mg/L (2.3 mmol/L) of choline in its various forms. (Holmes-McNary et al., 1996).

### *Intake from Supplements*

Choline is available as a dietary supplement as choline chloride or choline bitartrate and as lecithin, which usually contains approximately 25 percent phosphatidylcholine or 3 to 4 percent choline by weight. In the treatment of neurological diseases, large doses (5 to 30 g) of choline and phosphatidylcholine have been administered to humans (LSRO/FASEB, 1981). There are no reliable estimates of the frequency of use or amount of these dietary supplements consumed by individuals in the United States and Canada.

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## TOLERABLE UPPER INTAKE LEVELS

### *Hazard Identification*

#### *Adverse Effects*

Choline doses that are orders of magnitude greater than estimated intake from food have been associated with body odor, sweating, salivation, hypotension, and hepatotoxicity in humans (LSRO/FASEB, 1975, 1981). There are no indications in the literature that excess choline intake produces any additional adverse effects in humans. The animal data provide supportive evidence for a low degree of toxicity of choline. However, some animal studies have indicated growth suppression at high intakes (LSRO/FASEB, 1975). Because of the large doses and routes of administration used (e.g., intravenous and intraperitoneal injection), they were considered not relevant to human intakes from food and supplements (Davis, 1944; Hodge, 1945; Sahu, 1989; Sahu et al., 1986).

*Body Odor, Sweating, and Salivation.* High doses of choline have been associated with fishy body odor, vomiting, salivation, sweating, and gastrointestinal effects (LSRO/FASEB, 1981). These symptoms were reported in patients with tardive dyskinesia and cerebellar ataxia treated with choline chloride at 150 and 220 mg/kg of body weight/day for 2 to 6 weeks (10 and 16 g/day, respectively) (Davis et al., 1975; Growdon et al., 1977b; Lawrence et al., 1980). Studies of the production of methylamines from ingested choline suggest that fishy odor would have been observed in healthy populations (Zeisel et al., 1983). Fishy body odor results from the excretion of excessive amounts of trimethylamine, a choline metabolite, as the result of bacterial action. Lecithin, a choline-containing phospholipid, does not present a risk of fishy body odor because it generates little methylamine because the bacterial enzyme cannot cleave the ester (Zeisel et al., 1983).

*Hypotension.* Oral administration of 10 g/day of choline chloride (which is equivalent to 7.5 g [72 mmol] of choline alone) had a slight hypotensive effect in humans (Boyd et al., 1977). Choline could be acting by increasing vagal tone to the heart or by dilating arterioles. Although added choline increases acetylcholine release from in vitro preparations of heart (Loffelholz, 1981), changes in cardiac rate have not been observed in healthy humans treated with choline.

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*Hepatotoxicity.* Mild hepatotoxicity was reported in patients receiving choline magnesium trisalicylate (1,500 mg twice daily for 8 days) (Cersosimo and Matthews, 1987). There is also one reported case of severe hypersensitivity hepatitis with striking tissue and peripheral eosinophilia after ingestion of choline magnesium trisalicylate (Nadkarni et al., 1992). However, it is likely that hepatotoxicity was induced by salicylate rather than by choline (Cersosimo and Matthews, 1987). Humans with and without cirrhosis have been treated with large doses of choline chloride (6 g/day for 4 weeks) with no resultant liver toxicity (Chawla et al., 1989).

*Nonspecific Toxicity.* Tinnitus and pruritus have been reported in patients treated with doses of 3 g/day of choline magnesium trisalicylate for 6 weeks. These side effects were transient and probably caused by salicylate (Mody et al., 1983). The salicylate effect likely accounts for many of these observations, and the others are likely unusual anomalies, such as the one case of contact dermatitis reported after dermal exposure to choline chloride (Fischer, 1984).

### *Identification of Sensitive Subpopulations*

Individuals with trimethylaminuria (fish odor syndrome), renal disease, liver disease, depression, and Parkinson's disease may have increased susceptibility to the adverse effects of choline. Trimethylaminuria results from a rare genetic deficiency that causes excessive excretion of trimethylamine and, therefore, an increased risk of developing fishy body odor (Al-Waiz et al., 1988, 1989; Humbert et al., 1970; Shelley and Shelley, 1984). Individuals with renal or liver disease may have increased susceptibility because of increased levels of plasma choline (after ingestion of supplemental choline) compared with healthy individuals (Acara and Rennick, 1973; Acara et al., 1983; Chawla et al., 1989; Rennick et al., 1976). In rare cases, consumption of large amounts of choline has been associated with depression (Davis et al., 1979; Tamminga et al., 1976). Finally, mild and transient Parkinsonian signs (bradykinesia, tremor, and rigidity) were observed at high doses (12.7 g/day) of choline as a chloride in people with tardive dyskinesia (Gelenberg et al., 1979), which suggests that supplemental choline intake by Parkinsonian patients may exacerbate symptoms.

### *Summary*

On the basis of considerations of causality, relevance, and the

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quality and completeness of the database, hypotension was selected as the critical effect in deriving a Tolerable Upper Intake Level (UL); fishy body odor was selected as the secondary consideration.

### *Dose-Response Assessment*

#### *Adults*

*Data Selection.* The data used to derive the UL for choline include a single case report of hypotension and several other studies involving cholinergic effects and fishy body odor after oral administration of large choline doses.

*Identification of a no-observed-adverse-effect level (NOAEL) and a lowest-observed-adverse-effect level (LOAEL).* There are no adequate data demonstrating a NOAEL for excess choline intake. A LOAEL of approximately 7.5 g/day of choline can be identified from evaluation of a pilot study that reported hypotension in seven patients treated with choline for Alzheimer senile dementia (Boyd et al., 1977) and reports of fishy body odor in individuals treated with choline for tardive dyskinesia and Huntington's disease (Gelenberg et al., 1979; Growdon et al., 1977a, b; Lawrence et al., 1980). Boyd et al. (1977) treated seven older adult patients with 4 g/day of oral choline as choline chloride for 2 weeks followed by 2 weeks of choline at 7.5 g/day. At 4 g/day of choline, daily blood pressure recordings revealed no hypotension. In addition, there were no reports of nausea or diarrhea or other evidence of cholinergic effects at this dose level. At 7.5 g/day of choline, nausea, diarrhea, and a small decrease in blood pressure were reported in some patients. Other supportive data on cholinergic effects and fishy body odor after excess choline intake are summarized in Table 12-1.

*Uncertainty Assessment.* An uncertainty factor (UF) of 2 was selected because of the limited data regarding hypotension and the interindividual variation in response to cholinergic effects.

*Derivation of a UL.* A LOAEL of 7.5 g/day was divided by an UF of 2 to obtain a UL of 3.75 for adults, which was rounded down to 3.5 g/day.

#### *Choline UL Summary, Adults*

Because of the scarcity of data for any adult age group and

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**TABLE 12-1** Studies Reporting on Cholinergic Effects and Fishy Body Odor after Excess Choline Intake

| Study | No. of Subjects | Dose | Duration (wk) | Adverse Effects |
|---|---|---|---|---|
| Growdon et al., 1977a[a] | 20 | 9 g/d (wk 1); 12 g/d (wk 2)[b,c] | 2 | Mild cholinergic toxicity: lacrimation, blurred vision, anorexia, and diarrhea. |
| Growdon et al., 1977b | 10 | 8–20 g/d[d] | 2–17 | Fishy body odor in all subjects; at 250–300 mg/kg/d, produced lacrimation, anorexia, vomiting, and diarrhea. |
| Gelenberg et al., 1979[e] | 5 | 8–19 g/d[d] | 6–8 | 100% with fishy body odor after several days; gastrointestinal irritation.[f] |
| Lawrence et al., 1980[g] | 14 | 0.2 g/d (3 wk); 9 g/d (3 wk)[c,d] | 6 | At 150 mg/kg/d: 5 of 14 with fishy body odor; 12 of 15 with nausea and diarrhea. |

[a] Study involved a double-blind, crossover protocol.
[b] Choline was given as a chloride or bitartrate.
[c] Doses were calculated from data in the report using a reference body weight of 61 kg. Depending on the body weights of the individuals in Lawrence et al. (1980) and Growdon et al. (1977a), the lowest-effect dose may be less than 7.5 g/d.
[d] Choline was given as a chloride.
[e] Nonblinded study; did not include a control group.
[f] Mild, transient Parkinsonian signs (bradykinesia, tremor, and rigidity) were also reported.
[g] Double-blind protocol; included control group.

because no specific physiological function might be expected to affect sensitivity to excess amounts of choline in older persons, no adjustments are proposed for the elderly.

**UL for Adults 19 years and older 3.5 g/day of choline**

### *Other Life Stage Groups*

For infants, the UL was judged not determinable because of lack of data concerning adverse effects in this age group and concern

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about the infant's ability to handle excess amounts. The only source of intake for infants should be from food or formula to prevent high levels of intake. There are no data to suggest that during pregnancy or lactation increased susceptibility to developing cholinergic effects or fishy body odor from excess choline intake would occur. Therefore, the UL of 3.5 g/day is also set for pregnant and lactating women. The UL of 3.5 g/day for adults was adjusted for children and adolescents on the basis of relative body weight as described in Chapter 3, with the use of reference weights from Chapter 1, Table 1-2. Values have been rounded down.

*Choline UL Summary, Other Life Stage Groups*

| | | |
|---|---|---|
| **UL For Infants 0–12 months** | **Not possible to establish; source of intake should be formula and food only** | |
| **UL for Children** | **1–3 years** | **1 g/day of choline** |
| | **4–8 years** | **1 g/day of choline** |
| | **9–13 years** | **2 g/day of choline** |
| **UL for Adolescents** | **14–18 years** | **3 g/day of choline** |
| **UL for Pregnancy** | **14–18 years** | **3 g/day of choline** |
| | **19 years and older** | **3.5 g/day of choline** |
| **UL for Lactation** | **14–18 years** | **3 g/day of choline** |
| | **19 years and older** | **3.5 g/day of choline** |

*Special Considerations*

Individuals with the following conditions may be at risk of adverse effects with choline intakes at the UL: trimethylaminuria, renal disease, liver disease, depression, and Parkinson's disease.

### *Intake Assessment*

National surveys do not provide data on the dietary intake of choline. The UL applies to the weight of the choline moiety in the compound; for example, choline chloride contains more choline by weight than does choline bitartrate. Dietary supplements containing choline are available; however, reliable estimates of the

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amount of these supplements consumed in the United States and Canada are unavailable.

### *Risk Characterization*

Because there is no information from national surveys on choline intakes or on supplement usage, the risk of adverse effects within the United States or Canada can not be characterized.

## RESEARCH RECOMMENDATIONS FOR CHOLINE

### *High Priority Recommendations*

Sufficient human data are not available for determining whether choline is essential in the human diet, how much is required if it is essential, and the public health impact of poor choline nutriture. For this reason, research that could provide such human data is assigned the highest priority:

- Examination of the effects of the use of graded levels of dietary intake of choline on parameters of health. This would include assessing plasma and tissue choline compounds and metabolites; plasma cholesterol and homocysteine concentrations; erythrocyte folate; and liver, renal, brain, and other organ function. To facilitate this process, food composition data are needed for choline, phosphocholine, glycerophosphocholine, sphingomyelin, phosphatidylcholine, and betaine and the analytic sensitivity and specificity of methods for analysis of food composition need to be validated.
- Human studies on interrelationships among requirements for choline, methionine, folate, vitamin $B_6$, and vitamin $B_{12}$ to compare the homocysteine-lowering effects of combinations of these nutrients.

### *Other Research Areas*

Two additional topics also merit attention:

- The relative effectiveness of different choline-containing compounds in the diet in promoting health and determination of the sparing effect of endogenous synthesis of choline. It will be important to conduct studies on the bioavailability of choline and choline compounds and on the rate of de novo synthesis of choline in vivo.
- Studies using increasing levels of dietary intake designed to assess toxicity for all organ systems, including heart, liver, brain and

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kidney; fishy body odor; and possible growth suppression in children from observational data and as determined by experimental studies in animal models.

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